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THE EVOLUTION OF MODERN THERAPEUTICS*

BY

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It is not only quite logical that treatment should come last in a textbook description of diseases; it also follows the historical sequence of our knowledge. Fifty years ago it must be admitted that this section was very summarily dealt with, often consisting merely of vague statements. Nor is this surprising, when we were taught that in treatment "the first thing is diagnosis, the second diagnosis, and the third diagnosis." We should agree that the first thing is diagnosis, but if treatment stops there we should rightly find a dissatisfied patient.

Let me go back very briefly to the beginning. In Ancient Greece we find two cults side by side: the Aesculapian, with its methods of psychotherapy and suggestion; the Hippocratic, observational but dominated by the doctrine of the four humours—not much stress on medicines, though Hippocrates prescribed ox liver for anaemia. But both cults laid great emphasis on cleanliness, fresh air, attractive surroundings, and, where practicable, exercises. Galen placed much more reliance on drugs, as we are reminded by the persistence of the term "galenicals" in pharmacy. He carried the doctrine of humours to the point of saying that if, for instance, the patient was hot and wet, the appropriate treatment was cold and dry, thereby showing himself more of an "allopath" than the homoeopaths declare us to be.

After Galen comes the crash, and any attempt at medical science virtually vanishes from Europe. The reason is clear: in the Roman Empire, which was synonymous with the civilized world, physicians came to be treated as slaves, and medicine can flourish only in an atmosphere of freedom. Hippocratic medicine, it is true, flickered still at Salerno; for the rest, it was just kept alive by the Arabs. Otherwise there was a reversion to magic and witchcraft, with no real advance for more than a thousand years. True, a number of useful drugs derive from witchcraft and folklore, such as belladonna, hyoscyamus, aconite, valerian, cinchona, and digitalis.

The Beginnings of Scientific Medicine

Scientific medicine begins with the Renaissance—with the anatomy of Vesalius, the experimental methods of Gilbert, the physiology of Harvey, and the morbid anatomy of Malpighi. But their application to clinical medicine could scarcely be made effective while chemistry remained in such a confused and elementary condition. The crude attempts of the iatrochemists, such as Sylvius, came to very little. Meanwhile observational clinical methods made advance under Glisson, Willis, and Sydenham. Yet treatment could hardly advance until a more scientific study of drugs was made in the middle of the 18th century by William Heberden, who lectured on materia medica at St. John's College for ten years and did his best to found a rational pharmacology.

Still, it remains true, as Sir Francis Fraser says, that the beginning of the 19th century found treatment much the same as 1,500 years previously. The fundamental idea of disease as something added to the body, which had to be got rid of, still ruled the practice of therapeutics, which was therefore largely of an eliminative character—emetics, purgatives, diuretics, diaphoretics, and bleeding. As a better appreciation of the complex changes in disease developed, doubts gradually arose as to the wisdom of such heroic efforts to expel the disease from the body. It is not fanciful to see in this idea of expulsion an unconscious persistence of the more primitive idea of disease as due to demoniacal possession or influence.

With the 19th century came new methods of diagnosis—auscultation and percussion—which certainly made medicine more scientific. This led to a close comparison between the physical signs detected during life and the lesions revealed post mortem. In this way a solid body of knowledge was built up, but it led to some neglect of therapeutics by diverting attention from the beginnings of disease to its end-results, which produced a nihilistic attitude towards treatment by drugs. A rather comic sidelight is thrown on this aspect, that when I became medical registrar at Bart's the post-mortem book was still labelled "Register of Complete Cases." There you have it: no case complete until the necropsy is reached! Meanwhile anaesthetics and antiseptics were enabling surgery to shoot ahead.

It was not until the last quarter of the 19th century that therapeutics began to take a new course. Although salicylate had been synthesized for commercial purposes in 1874, the first synthetic preparation used clinically was antipyrine, or phenazone as it is now more usually called, which was prepared in 1883 by Filehne, whom I remember when he came here a few years later to work at antipyretics. The name "phenazone" has the advantage of reminding us that it, like salicylate, is a phenol derivative and therefore contains a benzene ring. It is very interesting to observe this in the earliest artificial products designed to influence metabolism, for a good many years were to elapse before it was found that a benzene ring or rings were an essential basis for products formed by the body to regulate its own metabolism. Thus adrenaline contains one such ring and thyroxine two, while the sex hormones and vitamin D contain four, condensed into the so-called phenanthrene ring.

The Biological Approach

The last decade of the 19th century saw yet a newer approach in therapeutics—the biological one, as seen in immunology and endocrinology. G. R. Murray introduced thyroid therapy in 1891, and active extracts of the adrenals and pituitary followed within the next few years. Hitherto the ductless glands had been regarded as excretory in character, the elimination theory cropping up again in a new guise. The bloated aspect of the myxoedematous patient might well suggest this; but Addison's disease was regarded as a failure on the part of the adrenals—anatomically so close to the kidneys—to detoxicate the body, until Sir Humphry Rolleston in his Goulstonian Lectures for 1895 adduced the evidence of its being an "atony" due to the loss of an internal secretion, the existence of which he predicted. And even quite recently hyperparathyroidism was attributed to a failure to eliminate guanidine. However, the conception of internal secretion, hitherto vaguely and fitfully held, was firmly established by Starling's hormone theory, which he put forward in his Croonian Lectures for 1905. This, by showing that the body prepared active chemical substances for its own use, had a marked influence in restoring

* A presidential address to the Cambridge Medical Society.

belief in the efficacy of drugs to influence its reactions. But no wave of advance is without a backwash, and the early triumphs of thyroid therapy misled us into thinking the problem simpler than it has proved to be. Moreover, a new polypharmacy arose, and I have seen prescriptions of an extraordinary conglomeration of animal extracts, quite unrelated to any evidence of their activity. Such abuses were a partial justification for Swale Vincent's sweeping declaration that organotherapy was administration of extracts of unknown value to a credulous patient by a still more credulous physician! Fortunately a more scientific attitude prevails to-day, and we have also learned not only that endocrines can influence the nervous system but that the converse is also true.

The other great advance in biological therapeutics—immunology—was, of course, an extension of the old empirical treatment of smallpox, first by inoculation and then by vaccination. The bacterial conception of disease gave a great impetus to research on these lines. Pasteur's work on rabies was the first scientific approach, but 1892 saw the early triumph of diphtheria antitoxin, and I recall with interest that two years later I was clinical clerk to the first patient to be treated by it in this country. You will not expect me to deal with the niceties of active and passive immunity. It would generally be agreed now that the passive immunity conferred by sera is suitable for acute diseases, while active immunity achieved by vaccines is principally useful in prophylaxis. Vaccines for established disease have, on the whole, proved disappointing, and I expect that most of my hearers find they are using them much less than 10 to 20 years ago. Routine inoculation by normal intestinal flora is, I hope, discarded: after all, it is a poor bowel that can't grow anything! In parenthesis it is an entertaining illustration of the changed point of view to read again Bernard Shaw's *Doctor Dilemma*; its contempt for clinical medicine and its emphasis on the marvels of opsonins read strangely to-day; for whoever hears of opsonins now? Nothing becomes out of date so quickly as the very up-to-date. Conclusions in clinical observations are difficult to reach, but, once achieved, they have a way of persisting. Thus in my professional lifetime the laboratory has given three different interpretations of Addison's disease, but no one has surpassed his clinical description of it.

Recognition of Deficiency Diseases

But to resume my main thesis: immunology and endocrinology had as their underlying principle the application of Nature's methods so far as was possible. The next step, for which we had to wait until the 20th century, was the recognition of deficiency diseases—the realization that, as it were, a minus could cause a disease as well as a plus. Not only has their study given us new therapeutical weapons, but it has given us new insight into the chemistry of the cell, which employs vitamins as powerful and essential catalytic agents. Endogenous catalytic agents we had recognized, and Garrod traced most inborn errors of metabolism to a congenital absence of one or another such agent. But here were exogenous catalysts; acquired needs as the biochemistry of the body became increasingly complex. As an example let me take R. A. Peters's work on vitamin B_1. Of all tissues in the body the brain cells are most sensitive to oxygen lack, and this intracellular oxygen is supplied by dextrose. If an overdose of insulin has locked up too much of this for the metabolic needs of the moment the patient is convulsed and then becomes unconscious. This we knew; but Peters showed that vitamin B_1—aneurin—is necessary to the breakdown of dextrose so that its oxygen is presented in a suitable form for the brain cell to accept.

We owe, indeed, a great debt to the biochemist and the organic chemist. The latter has provided us with an enormous number of synthetic remedies, while, linked with the biochemist, he not only has unravelled the complexity of, for instance, the structure of the sex hormones, but has actually produced artificially substances of a simpler constitution and yet more potent than the natural ones. If you ask why did not Nature make them, the answer is ready to hand. The natural product has to be prepared within rigid limits of temperature and *p*H. The laboratory methods would often be fatal to the survival of the cell.

The Action of Drugs: A New Conception

I now come to a line of work which seems to me to have introduced a new conception of the action of drugs and has led to a new generalization: that every nervous stimulus to the tissues is mediated through a chemical reaction. The outline of the history of these researches is interesting. In 1901, soon after the isolation of adrenaline, Langley pointed out that its effect on any tissues was the same as if the sympathetic nerve to that part had been stimulated; but the enormous significance of this observation was not realized for some years. In 1906 Langley and T. R. Elliott independently found it necessary to postulate the existence of a receptive substance between the nerve ending and the tissue supplied. It had long been known that in many instances atropine would block the passage of a nervous impulse, while pilocarpine or physostigmine would facilitate its passage and increase the response. Thanks to Dale and to Loewi, these observations were combined and extended to reach a striking conclusion. It was found that when a sympathetic nerve was stimulated adrenaline was liberated at the post-ganglionic nerve ending. This explains Langley's observation and enables us to realize that the adrenal medulla contains an emergency store of adrenaline to motivate widespread sympathetic effects when necessary. The other nerve endings of the nervous system liberate acetylcholine, which activates the appropriate tissue. Thus we can divide the nerve endings into adrenergic and cholinergic, according as they liberate adrenaline or acetylcholine.

Now when atropine paralyses the vagus, for example, it does so by preventing acetylcholine from getting into the receptive substance, though just as much of it is produced as before; and when physostigmine—or eserine, as it is more usually called—prolongs or intensifies the effect of parasympathetic stimulation it does so by preventing the destruction of the acetylcholine set free. The pharmacology of the future will have to study the natural history of these receptive substances and find out in what way they can be helped by drugs, both positively by facilitating their reactions, and negatively by blocking the way against the entrance of toxins.

Attempts to utilize acetylcholine therapeutically have been disappointing and have led to a search for more satisfactory synthetic substitutes. By varying their composition it might also be possible to produce more selective reactions. Of such doryl—otherwise known as carbachol—and mecholin are examples which have met with some limited success. On the adrenergic side ephedrine and benzedrine are familiar examples of drugs which imitate sympathetic action, though there are several other examples that have hardly come as yet into general use. We are getting to know more about their absorption and fate in the body, and in future more uses for them may be found.

Turning to the other side of such reactions, we find, for instance, in eumydrine and prostigmin synthetic drugs which have a more selective action than their native congeners in blocking or facilitating the action of acetylcholine. Eumydrine, which is the methyl nitrate of atropine, is particularly useful in relaxing pyloric spasm. Like physostigmine, prostigmin prevents destruction of acetylcholine at the end-plate, but for a much longer period. Dr. Mary Walker introduced its use in myasthenia gravis, which we may now attribute to some toxic substance—produced by a diseased or, at any rate, an enlarged thymus—which has a curare-like effect in blocking the end-plate between nerve and muscle. The clearing up of this point has naturally encouraged surgeons to treat myasthenia gravis by thymectomy, and Geoffrey Keynes has performed the operation 28 times. The results are variable but in some cases very successful, though the ultimate elimination of the toxin may not be effected even for several months after operation. It is an interesting example of the biochemist indicating the scientific basis to justify the intervention of the surgeon.

We see, then, that drugs may help or bar the entrance of stimuli into the cell. Another way in which they may have this effect is by adsorption on to the cell envelope: thus the barbiturates oppose the entrance of thyroxine, and it is interesting to recall that practitioners were using them empirically before this action was known. A much more selective action

against thyroxine is provided by the new drug thiouracil, but its therapeutic effects are still on trial. Its discovery has, however, called attention to other selective actions against endocrines, such as alloxan against insulin and the temporarily sterilizing effect of sulphapyridine in males, while thallium salts appear to be specific against the whole endocrine system. The only therapeutic value in these latter substances is the possible treatment by alloxan of spontaneous hypoglycaemia from hyperinsulinism.

Chemotherapy

The last great advance, chemotherapy, is so much in the news to-day that I need refer only to certain general principles involved. When, in 1907, Ehrlich put forward his theory of side chains, haptophores, and amboceptors to account for the formation of antitoxins, it was, after a preliminary welcome, rather discounted as the kind of thing a German would evolve out of his own inner consciousness. Yet it contained a germ which very soon grew into chemotherapy, for there was the idea of a chemical substance attaching itself to some link in the invading microbe and thus completely sterilizing it. Salvarsan was the result, and, although it has not fulfilled the expectation of its discoverer that it would cure syphilis in one dose, it has proved to be the greatest advance in the treatment of that disease. Ehrlich, as we know, was profoundly interested in dyes, and it was the *intra-vitam* selective staining by methylene blue which gave him the original idea. This is doubly interesting, since it was the dye industry which gave us sulphonamide. This substance was synthesized in 1908 and employed to increase the fastness of dyes. It was thought that this quality was due to the union of the substance with the protein cells of the wool. Although in 1919 some of such dyes were noted to be bactericidal, no clinical application of this observation was begun till 1930, when prontosil was reported upon favourably in the treatment of erysipelas and Domagk came to the conclusion that it had no effect *in vitro* but acted only in living tissues. Later work shows that the action of the sulphonamides must be regarded not as bactericidal but as bacteriostatic, holding the growth of bacteria up until the natural defences of the body could come into action. We now know more of the way in which this is accomplished, for it has been shown that sulphonamides successfully compete with *p*-animobenzoic acid for the favours of the cell, and thus literally starve the bacteria into surrender if present in sufficient concentration.

I have pointed out that since the 'nineties the trend of therapeutics had been towards applying Nature's own methods, and chemotherapy at first appeared a diversion in an entirely different direction. Now it is seen that sulphonamides act, as one may say, biologically, producing a deficiency disease in bacteria. In a sense earlier observations on salvarsan pointed to a similar conclusion, for just as the body can be educated by small doses of a toxin to resist larger doses, so the *Spirochaeta pallida* can become resistant to bigger doses of salvarsan if first given inadequate ones.

The multiplication of sulphonamide derivatives goes on apace, and already sulphapyridine has been displaced as first favourite, even against the pneumococcus, by sulphadiazine and sulphathiazole. I need not go into details beyond mentioning that, clearly, when a local action is required the less soluble forms are preferable; thus for dysentery sulphaguanidine is the drug of election.

The sulphonamides are not the only drugs to show bacteriostatic powers: gramicidin, for instance, is a crystalline polypeptide intensely toxic to pneumococci and haemolytic streptococci. The underlying principle is the same: to attach linkages to the main agent in such a way as to diminish its toxic and to increase its therapeutic effect. Thus salvarsan contains enough arsenic to be violently toxic if it had not been linked with certain organic groups. We have an instance of this in a drug which does not come within the present definition of chemotherapy; I mean salyrgan or, to give it the official name, mersalyl. It has long been known that mercury is toxic to the convoluted tubules of the kidney, and if given in sufficient strength can necrose them. Yet its organic compound mersalyl is used as a diuretic. Apparently it does so by throwing the absorptive power of the tubules out of action while allowing filtration to go on unhindered, with the result that a large quantity of dilute urine is passed. The toxic action of mercury has been greatly reduced, but it must be observed that it is still acting in a mild and selective way against the efficiency of the tubules to concentrate, and is thus a risky diuretic in kidney diseases.

The aim in chemotherapy may be said to be achieved when the toxic action of the drug is practically *nil* and its therapeutic effect is at the maximum. It is easy to prepare an antiseptic strong enough to destroy bacteria, but the tissues of the host would be damaged to a varying extent. Penicillin seems to have achieved the desired end of bacteriostasis without any such toxicity. It is only one of a whole series of such agents elaborated by micro-organisms and fungi, but is so far the best and most easily handled. By this time we have become familiarized with both its successes and its limitations. We know that its antibiotic power can be exercised in dilutions of one part in a million, and in its pure form even one in 50 millions. Like other chemotherapeutic agents, it differs from antiseptics in that it selectively attacks the organism causing the disease without doing serious injury to the tissues. We can now realize that, in malaria, quinine acts in exactly the way of a chemotherapeutic agent.

The discovery of penicillin by Fleming illustrates Pasteur's dictum that chance enters only the mind that is prepared. Many people, including Pasteur himself, must have seen their culture plates contaminated by moulds, but only Fleming saw the significance of the sterile ring surrounding the spot of contamination. However, just as it required Best to turn Banting's discovery of insulin to practical purposes, so have Florey's researches achieved this for Fleming's discovery.

The Endocrine Orchestra

To turn to an entirely different development of therapeutics: 12 years ago I delivered myself of the statement that the pituitary was the leader of the endocrine orchestra—a statement frequently repeated since. To-day I would add: and the hypothalamus is the conductor, for in the interval it has become clearer that the endocrine system is much more influenced by the nervous centres for emotional expression in the hypothalamus than was recognized 12 years ago. For an important part of this knowledge we are indebted to the anatomists. My analogy fails at one point, for in some ways the hypothalamus and the anterior pituitary form one unit, and diabetes insipidus, for instance, may result from a disorder of any part of it. But, changing the metaphor, we have in the pituitary a great transformer of nervous into chemical activity, which in its turn stimulates or inhibits other ductless glands by the appropriate trophic hormone. The hypothalamus in its turn receives impulses from the cortex, so that the psychic state can play on the endocrines through the pituitary, just as the endocrines can modify the psychic state. One has only to think of the influence of hyperthyroidism or hypogonadism to realize that. It is not a one-way traffic between cortex, hypothalamus, and endocrines. This conception has greatly added to the interest in the treatment of mental states by physical means, which well accords with the prevalent psychosomatic view of disease in general. So the benefit of insulin-produced convulsions—accidentally discovered, I believe—fitted into the picture. Originally used for schizophrenia, they were soon replaced by electrically induced convulsions. The present view, I gather, is that insulin is still to be preferred for schizophrenia, but electricity for autonomous depression. The success of the latter is undoubted, but of the former more variable. And the electric method has far fewer unpleasant side-effects. It is difficult to see how the benefit is conferred, but it looks as if the violent convulsions may break down some resistances between association cells. Now that the surgeon is taking a hand and performing leucotomy, and is claiming successes, it would certainly appear that *something* at any rate is broken down. It is not surprising to learn that leucotomy is sometimes followed by a lack of initiative and tact, though intelligence and artistic capacity are claimed on occasion to be actually increased. It has been stated that the fundamental change is a diminution of self-consciousness, as if a pathological point in the cortex had been cut off from its mental connexions. To me it seems a desperate remedy, to be reserved for desperate cases.

Other physical methods in the treatment of psychoneuroses and psychoses include continued narcosis and partial loss of consciousness under light anaesthesia. The latter procedure is used for recovery of buried memories by hypnotic suggestion during the recovery period.

Psychological Aspects of Disease

But such methods are for the severest types of cases. The point which concerns all of us is the striking change from the materialistic outlook prevalent in my student days to the modern recognition of the psychological aspects of disease. On this let me quote Sir Francis Fraser, himself trained in the strictest sect of organic medicine. Speaking of the criticism that the medical schools give too scientific a training and send men out knowing next to nothing of the care of patients or of the personal side of practice, he says: "I am sure it is a just criticism, but maintain that hospital practice is not 'too scientific'—it is not sufficiently scientific. . . . Treatment based on the deduction that one patient's inefficiency is due to family troubles is just as scientific as that based on *x*-ray evidence of duodenal ulcer in another patient. To say 'there is nothing the matter' because the physical examination, *x*-ray evidence, and laboratory tests fail to disclose a cause of the trouble is, on the other hand, unscientific. If there was more exact knowledge of how the material and mental surroundings of our patients affect their functions and activities . . . clinical instruction would more nearly meet the needs of private practice, and it would be more scientific, not less."

This was written 10 years ago, and I am sure that the author would admit that since then it has been shown that the psychological factor plays a considerable part in the causation even of the organic lesion he selects—duodenal ulcer. And so the latest phase in the evolution of modern therapeutics is recognition of the psychosomatic factors in disease—thereby in a way completing the circle by a return to Aesculapius.

Discarded Methods

The path of this progress is littered on either side by discarded theories and practices. It is a chastening experience to turn over one's old case records. One suddenly realizes that some formerly favourite treatment has been completely forgotten. My belief is that we practise continually an almost unconscious revision, and in this way a consensus of opinion is reached: no one has openly attacked the treatment, perhaps—it has just passed silently into oblivion. And I suspect that a scrutiny of past literature from manufacturing firms would show that they have found it advisable to cease making a good many formerly vaunted remedies.

On this matter Trousseau's advice to his students remains as true as on the day when it was spoken: "Always use the new remedies while they still have power to heal." How is it that people were formerly cured by Bulgarian soured milk or by Bulgarian belladonna and are no longer? How is it that the routine use of vaccines therapeutically is fading out while their prophylactic use is increasing? One could quote many such examples. I think that admirable clinician the late T. A. Ross supplied the explanation. He noted that his experience of the result of the Weir Mitchell treatment fell into three periods. In the first the results were excellent and in the second variable; the third group was a failure. Then he realized that in the first he himself firmly believed in the method, in the second he had come to doubt it, while in the third he had ceased to believe in it and used it only at the request of others. I had the opportunity of studying Sir Lauder Brunton's methods fairly closely nearly 50 years ago. I attributed his undoubted therapeutic successes to two things—he had a genuine and deep sympathy for human suffering, and he always felt sure that he knew the precise remedy—preferably a new one from Germany—which would exactly suit the individual patient.

Conclusion

Well, I hope I have been able to show that gradually and by painstaking effort the profession has come into possession of a much larger number of well-attested remedies than formerly, in which we can have enough confidence ourselves justifiably to inspire confidence in our patients. We have a much clearer view of the fundamental principles of therapeutics, and the present position is full of promise for the future, for the last 40 years have shown greater advance than all the preceding centuries. We have passed away from the ancient mixture of empiricism and magic, by way of pharmacology, to a biological and indeed a biochemical approach. The tree of healing can now draw sustenance from many roots. In its present state it is still a young growth; let us see to it that its development is healthy, strong, pruned, and, above all things, honest.

SCABIES PROPHYLAXIS USING "TETMOSOL" SOAP

BY

KENNETH MELLANBY, Sc.D.

Recently I described (Mellanby, 1944a) some experiments in which attempts were made to control scabies infection. Except where therapeutic treatment with benzyl benzoate was given to all members of a closed community the results were disappointing. Since that paper was written a new method of some promise has been described (Davey *et al.*, 1944; Gordon *et al.*, 1944), and the present article describes a further prophylactic trial.

Prof. R. M. Gordon and his colleagues, in conjunction with Imperial Chemicals (Pharmaceuticals) Ltd. and Unilever Ltd., have produced a soap with good cosmetic properties which contains 10% of "tetmosol" (i.e., tetraethylthiuram monosulphide). The use of this soap has been shown to kill *Sarcoptes* and thus to cure scabies, though as a therapeutic agent at a treatment centre it is less efficient than benzyl benzoate. It is, however, so simple to use that it seemed possible that its general issue to an infected population would prevent further transmission of the disease. Whereas these authors described the therapeutic effect of tetmosol soap, they expressed the belief that its greatest value would be found in its use as a prophylactic against scabies—a property which they had already proved in the case of animals.

For a satisfactory test of the prophylactic value of tetmosol soap it was necessary to have a population showing a high incidence of scabies and to ensure that the soap was used by all individuals. Furthermore, facilities must be available for examining all subjects before and after the period during which the soap was used, in order to assess the effect on the incidence of scabies. Such conditions were found in a large mental hospital. Scabies was endemic among the patients; and the staff, having had many difficulties in combating the disease, were only too willing to co-operate in an experiment which might alleviate the position. To assess the amount of scabies present before, during, and after the experiment would obviously take a great many hours of skilled examination, but fortunately I had available at the Sorby Research Institute sufficient trained staff to make this practicable.

These facilities being available, I wished to place them at the disposal of Prof. Gordon. He decided, however, that he would prefer me to take the responsibility for the experiment, though he placed his advice at my disposal and also helped with the experiment in a number of ways.

Procedure

Before the experiment started every patient in the hospital was inspected; tetmosol soap was then supplied to approximately half of them. The details of the experiment were explained to the hospital staff, but nothing was said to the patients, who simply accepted the soap provided (it was rather pleasanter to use than that ordinarily available). All other treatment of scabies, whether in the control or in the experimental group, was discontinued for the 11 weeks of the trial.

Examination of the patients was carried out by volunteers from the Sorby Research Institute; these men had themselves had prolonged experimental infections with scabies, and were fully familiar with finding and removing acari. The examinations were all made under the supervision of Mr. W. C. Bartley. During the initial examinations I also was present, and during